IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) **DEMAND FOR JURY TRIAL**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff/Counter Defendants.	

EXHIBIT 15C

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 3 TO EXCLUDE TESTIMONY OF MICHELLE HASTINGS, PH.D. THAT IS CONTRARY TO LAW

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 3 TO EXCLUDE TESTIMONY OF MICHELLE HASTINGS, PH.D. THAT IS CONTRARY TO LAW

[redacted]

Counter-Plaintiffs Sarepta and UWA move under Fed. R. Evid. 402 and 403 to preclude NS's expert witness Dr. Michelle Hastings from testifying contrary to law and contrary to NS's representations to this Court. In particular, Dr. Hastings should not be permitted to testify regarding legally incorrect written description and enablement arguments that fail to account for ***all*** elements of the asserted claims of the Wilton Patents. Dr. Hastings also should not be permitted to testify about opinions of another NS expert, Dr. Wood, that he represented he would not give in this case. Testimony on both of these topics is prejudicial and should be excluded.

I. Dr. Hastings' Written Description and Enablement Arguments Are Contrary to Law

According to Dr. Hastings, the claims of the Wilton Patents are "essentially boundless" and thus are invalid for lack of written description and enablement. D.I. 427-5, ¶¶ 49, 114. But Dr. Hastings ignores well-settled law that ***all*** claim elements must be considered for written description and enablement. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1348 (Fed. Cir. 2010) (the written description analysis ***compares the claims*** with the invention disclosed in the specification); *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988) ("The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the ***claimed invention***.") (emphasis added).

In particular, the Wilton Patents asserted by Sarepta in this action claim an "***antisense oligonucleotide*** . . . comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA"—and the independent claims refer to "antisense" oligonucleotide two more times. *E.g.,* D.I. 417-1 (Ex. 1), claim 1 (emphasis added). But Dr. Hastings disregards entirely the term "antisense" oligonucleotide, resulting in claims that would encompass oligonucleotides that are not "antisense." *See, e.g.*, D.I. 427-5, ¶ 45 (attributing no meaning to "antisense" oligonucleotide). *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1288 n.10 (Fed. Cir. 2017) ("It is highly disfavored to construe terms in a way

[redacted]

that renders them void, meaningless, or superfluous."). Her writing "antisense" out of the claims to argue invalidity is particularly egregious given that Dr. Hastings *agrees* with Sarepta's expert on the plain meaning of the term, and the Court did not construe it at *Markman* based on NS's representation that it was not in dispute. *See* D.I. 467 at 1-5; D.I. 248 at 6 ("The Court agrees with NS that only those terms actually in dispute require a construction. . . . Accordingly, because only particular terms of the Antisense Oligonucleotide Phrase are in dispute, the Court will only construe those disputed terms rather than the phrase as a whole.").[1] Dr. Hastings' written description and enablement arguments are contrary to law, would result in juror confusion, are prejudicial to Sarepta and UWA, and should be precluded for failing to apply the plain meaning of the term "antisense" oligonucleotide. *Huawei Techs., Co. v. Samsung Elecs. Co.*, 340 F. Supp. 3d 934, 965, n.21 (N.D. Cal. 2018) ("To the extent that any of these opinions are based on incorrect legal assumptions or propose views that diverge from the actual law, . . . those opinions may be excluded via motions *in limine*."); *Knauf Insulation, LLC v. Johns Manville Corp*., No. 1:15-cv-00111-TWP-MJD, 2023 WL 2726879, at *4-5 (S.D. Ind. Mar. 31, 2023) (granting motion in limine to exclude portions of expert reports that employed an inappropriate legal standard and "failed to consider the full" analysis required by law); *J&M Indus., Inc. v. Raven Indus., Inc*., 457 F. Supp. 3d 1022, 1048-49 (D. Kan. 2020) (granting a motion to exclude expert opinions on patent anticipation as "contrary to well-established law," and because of a "fail[ure] to show that [the expert's] opinion . . . was based on a proper application of the standards governing anticipation"); *Willis Elec. Co. v. Polygroup Macau Ltd. (BVI)*, 649 F. Supp. 3d 780, 807-808

[1] While NS has argued that Sarepta's expert Dr. Dowdy should be precluded from testifying regarding the plain meaning of "antisense" oligonucleotide, Dr. Hastings impermissibly ignores this term. D.I. 467 at 1-5.

(D. Minn. 2023) (excluding an expert's opinions regarding specific claim terms as "contrary to law" because the opinions did not follow the claim language).

II. Dr. Hastings Should Be Precluded from Testifying about Opinions that Dr. Wood Swore He Would Not Give

In arguing that NS's expert Dr. Wood does not have a disqualifying conflict of interest based on work he had done for Sarepta,[2] Dr. Wood submitted a sworn declaration to this Court stating that he would not offer opinions concerning the "infringement or validity" of the Wilton Patents. D.I. 309, ¶ 3. Nevertheless, Dr. Wood then submitted expert reports addressing, *inter alia*, (1) unpredictability in the field, (2) what the inventors of the asserted patents allegedly invented, D.I. 385-1 (Ex. 1) at 34-49, (3) whether the Wilton Patents' specification resolved the unpredictability in the field, including whether the Wilton Patents' specification disclosed a "hot spot," D.I. 385-1 (Ex. 3) at 4-18, and (4) what a POSA would have concluded the inventors of the Wilton Patents "possessed." D.I. 385-1 (Ex. 3) at 18. Dr. Hastings then relied on Dr. Wood to argue that the Wilton Patents are invalid because "[a] POSA cannot envision what structural features are common to all members of the [Wilton] Patent claims," and "even antisense oligonucleotides sharing a common sequence of different lengths can exhibit a wide variety of exon skipping activity." *See* D.I. 427-5, ¶¶ 63, 117 (citing to Wood in support of alleged lack of written description and enablement). Dr. Hastings should be precluded from relying at trial on Dr. Wood's opinions in support of her contention that the Wilton Patents are invalid. Her reliance would be an end-run by NS around Dr. Wood's sworn declaration to the Court and would be prejudicial to Sarepta and UWA.

[2] This is the subject of pending motions (D.I. 298, D.I. 385, D.I. 393). To be clear, Sarepta and UWA are not seeking to preclude Dr. Hastings from testifying regarding purely technical tutorial topics such as explaining how exon skipping works.

[redacted]

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CERTIFICATION PURSUANT TO LOCAL RULE 7.1.1

Defendant and Counter-Plaintiffs Sarepta Therapeutics Inc. and the University of Western Australia certify that a reasonable effort has been made to reach agreement with Plaintiff and Counter-Defendants Nippon Shinyaku Co., Ltd. and NS Pharma, Inc. regarding Counter-Plaintiffs' Motion *in Limine* No. 3. The Parties were unable to reach agreement, and Counter-Defendants refused to agree to Counter-Plaintiffs' requested relief.

/s/ Megan E. Dellinger

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH)
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

[PROPOSED] ORDER GRANTING SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 3 TO EXCLUDE TESTIMONY OF MICHELLE HASTINGS, PH.D. THAT IS CONTRARY TO LAW

At Wilmington this _____ day of _____, 2024, having considered Defendant and Counter-Plaintiffs Sarepta Therapeutics, Inc. and the University of Western Australia's Motion *in Limine* No. 3 to Exclude Testimony of Michelle Hastings, Ph.D. That Are Contrary to Law, and all papers and arguments submitted therewith, IT IS ORDERED that the motion is GRANTED. Plaintiff and Counter-Defendants Nippon Shinyaku Co., Ltd. and NS Pharma, Inc. (collectively, "NS") expert witness, Dr. Michelle Hastings, is precluded from testifying contrary to law and contrary to NS's representations to this Court as set forth in the motion.

_____

United States District Judge

CERTIFICATE OF SERVICE

I hereby certify that on April 19, 2024, copies of the foregoing were caused to be served upon the following in the manner indicated:

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) **DEMAND FOR JURY TRIAL**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff/Counter Defendants.	

PLAINTIFF'S RESPONSE TO SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 3 TO EXCLUDE CERTAIN EXPERT TESTIMONY OF MICHELLE HASTINGS, PH.D.

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Dated: April 25, 2024

Dr. Hastings § 112 Opinions. Sarepta and UWA premise their motion on Dr. Dowdy's belated attempt to construe "antisense" counter to the Court's construction. Because Dr. Hastings alternatively analyzes written description and enablement under Dr. Dowdy's interpretation,[1] this motion only implicates Dr. Hastings's "trillions" genus calculation. Regardless, because Dr. Hastings applies the correct construction, the Court should deny this motion.

At claim construction, the parties disputed whether the claims required complementarity across the ***entire*** claimed ASO, or only a ***portion***.[2] D.I. 166 at 7. NS asserted the latter. *Id.* Sarepta and its expert were clear that "[u]nder NS's construction, a claimed antisense oligonucleotide can include ***a majority*** of non-complementary bases." *Id.* at 32-33; D.I. 159 ¶ 19 (Stein Rep. Decl.) (arguing that "[u]nder NS's construction," a "claimed" 31-mer ASO "could have 12 bases derived from SEQ ID NO: 195 (which would be 100% complementary) and ***19 bases*** that are completely unrelated to the dystrophin gene (which would have 0% complementary).").

The Court adopted NS's interpretation, D.I. 248 at 9-10, and Dr. Hastings applied it exactly as (even Sarepta and its expert) contemplated during claim construction. As she explains, the Court construed the "100% complementarity" limitation to apply only to the "base sequence," which need not span the entire ASO. D.I. 427-7 ¶ 41; D.I. 248 at 9-10. The UWA claims thus encompass ASOs comprising: (1) a "base sequence," *i.e.*, a portion of the ASO that is 100% complementary to a target region, and (2) a portion of the ASO outside of the "base sequence" that can, but need not be, 100% complementary. D.I. 427-7 ¶ 13; *see also* D.I. 421 at 2-3. Dr. Hastings did not ignore any claim limitation—she directly applied the Court's construction. And under that construction,

[1] Dr. Hastings opines that the UWA Patents are still invalid. *See, e.g.*, D.I. 427-7 ¶ 20 ("Dr. Dowdy's 'universe' of PMOs—whether it is based on allowing one or two mismatches—is simply too large for a POSA to immediately visualize or recognize each member of the genus claimed in the UWA Patents."); *id.* ¶ 67 ("Even practicing the full of scope of Dr. Dowdy's 'universe' of tens of thousands of AOs would have required a tremendous quantity of experimentation.").

[2] All emphases added unless otherwise stated.

the scope of the UWA claims is extremely broad. D.I. D.I. 427-7 ¶ 14.

In contrast, Sarepta replaced its claim construction expert (who had agreed the adopted construction allowed up to nineteen mismatches) with Dr. Dowdy, who admits he offers an entirely new construction for "antisense." D.I. 427-13 at 15:2-18. Dr. Dowdy's proposed "plain meaning" is an improper attempt to redo claim construction. Courts routinely preclude experts from re-arguing unsuccessful claim construction issues to the jury, even when disguised as a "plain meaning" argument (as Dr. Dowdy does here). *See, e.g.*, *Align Tech., Inc. v. 3Shape A/S*, No. 17-1646-LPS, 2020 WL 4926164, at *5 (D. Del. Aug. 14, 2020) (rejecting defendant's argument "that [its expert] is merely applying the plain and ordinary meaning of the claim term"); *EMC Corp. v. Pure Storage, Inc.*, No. 13-1985-RGA, 2016 WL 775742, at *4 (D. Del. Feb. 25, 2016) (excluding expert testimony citing "embodiments in a patent specification" because that argument "regarding the plain and ordinary meaning of claim terms would amount to claim construction"); *MediaTek Inc. v. Freescale Semiconductor, Inc.*, 2014 WL 971765, at *5 (N.D. Cal. Mar. 5, 2014) (excluding expert testimony that "relie[d] heavily" on intrinsic evidence to "expound upon a specific meaning and/or requirements of the terms identified").

Here, Dr. Dowdy relies on the same specification disclosures (col. 25, tbl. 1A) and prosecution history (SRPT-VYDS-0004781-99) that Sarepta cited during claim construction in support of its rejected construction. *Compare* D.I. 427-2 ¶¶ 38-39 *with* D.I. 166 at 32-33 and Ex. 1 (May 3, 2023 Hr'g Tr) at 22:22–23:7. The Court considered this intrinsic evidence during claim construction and determined that it did not limit the claims. *See* D.I. 248 at 10; *see also* D.I. 421 at 1-3; D.I. 494 at 1-2. Notably, Sarepta/UWA proposed construing "antisense" as part of Term 1, and yet agreed that the disputes over Terms 1a, 1b, and 1c were the ***only*** disputes. Hr'g Tr. (May 3, 2023) at 16:2-16. If Sarepta/UWA then-contended that the preamble language "antisense"

imposed a further limitation, they should have said so. But they did not, and still have made no effort to establish that "antisense" is limiting preamble language under the applicable standard.[3]

Dr. Hastings's Reliance on the Opinions of Dr. Wood. Sarepta also seeks to preclude reliance on Dr. Matthew Wood's opinions. What Sarepta elides is that Dr. Hastings relies on technological background from a publicly available declaration that ***Sarepta/UWA submitted*** to the PTAB regarding the state of the art—a declaration in which Dr. Wood offers a nearly-identical description to that in his Opening Report. D.I. 427-5 ¶¶ 63, 116, 117 (citing Wood Interference Decl., Ex. 2, ¶¶ 74 and 68-81). That publicly available declaration would have been available for NS and Dr. Hastings to rely on even if Dr. Wood was not involved in this litigation. There is no unfair prejudice from NS and Dr. Hastings relying on publicly-available testimony that Sarepta/UWA themselves sponsored. It is simply the natural result of Sarepta/UWA choosing to take positions in this litigation directly contradictory to their factual representations to the PTAB and the Patent Office to obtain the UWA Patents and other family members. [redacted]

This latest salvo seeks to erase Sarepta's prior, contradictory statements from the record under the false premise that NS cannot rely on even generic background information provided by Dr. Wood. In other words, it is another opportunistic attempt to exclude Dr. Wood entirely. That is the true end-run attempt here, which the Court should reject.

[3] It is not. The remaining claim recites a "structurally complete invention": the ASO's constituent "base sequence" interacts with a pre-mRNA "target region." *See Zimmer Surgical, Inc. v. Stryker Corp.*, No. 16-679-RGA, 2018 WL 3038515, at *4 (D. Del. June 19, 2018) (quoting *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002)). "Antisense" is merely a "descriptive name." *Id.* at *5 (quoting *Am. Med. Sys., Inc. v. Biolitec, Inc.*, 618 F.3d 1354, 1358-59 (Fed. Cir. 2010)).

Dated: April 25, 2024

Respectfully submitted,

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Exhibit 1 to NS's Response to Sarepta's MIL No. 3

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD.,	)	
Plaintiff,	)	
v.	)	
SAREPTA THERAPEUTICS, INC.,	)	
Defendant.	)	**C.A. No. 21-1015-GBW**
SAREPTA THERAPEUTICS, INC.,	)	
Defendant/Counter-Plaintiff,	)	
v.	)	
NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC.	)	
Plaintiff and Counter-Defendants.	)	

- - - -

Wilmington, Delaware
Wednesday, May 3, 2023
Markman Transcript

- - - -

BEFORE: HONORABLE GREGORY B. WILLIAMS
UNITED STATES DISTRICT COURT JUDGE

- - - -

Michele L. Rolfe, RPR, CRR

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- - - - -

PROCEEDINGS

(REPORTER'S NOTE: The following Markman was held in Courtroom 6B, beginning at 10:00 a.m.)

THE COURT: Good morning. You may be seated. All right. Let's start by having counsel put appearances on the record.

MS. DUDASH: Good morning, Your Honor. Amy Dudash from Morgan Lewis for plaintiff, Nippon Shinyaku. And with me here today is Amanda Williamson, Michael Sikera, Eric Kraeutler, Zachary Miller, Krista Venegas, as well as our client representative patent attorney from Nippon Shinyaku.

THE COURT: Good morning, all.

MS. DELLINGER: Good morning, Your Honor. Megan Dellinger of Morris Nichols of behalf of Sarepta and the University of Western Australia. And I'm joined this morning by my co-counsel from Finnegan Henderson, William Raich and Yoonjin Lee. And we also have with us this morning Mr. Mark Evans, who is in-house counsel at Sarepta.

THE COURT: All right. So we have a number of terms to construe today and we have two sets of briefs on the issues. We have -- we set aside three hours for this hearing. We'll start with the Wilton patents, so we'll start.

MR. RAICH: Thank you, Your Honor. We have printouts of our demonstratives, may we approach to deliver them?

THE COURT: Yes.

MR. RAICH: And, Your Honor, just by way of background, we've agreed to go term by term, so that's what we intend to do, unless you'd like something different.

THE COURT: No, term by term is typically how we do it.

MR. RAICH: Very good. Thank you. Bill Raich from Finnegan on behalf of defendant and counter-plaintiff Sarepta Therapeutics and The University of Western Australia.

So the Wilton patents disclose the pioneering work of Steve Wilton and colleagues at The University of Western Australia. It disclosed the first ever approved treatment for DMD and covered the first two FDA-approved treatments targeting exon 53. Sarepta's VYONDIS product, approved in 2019. And Nippon Shinyaku's VILTEPSO product approved the following year.

There are, as you know, three terms in dispute, shown with yellow, purple, and green highlighting on slide 3. And Nippon Shinyaku has identified three subterms that it believes should be separately construed.

And the disputed phrases work in unison to

structurally describe the claimed antisense oligonucleotide, thus construing them in the context of the claimed invention as a whole just makes sense.

That's also consistent with the Federal Circuit's guiding principal, the context of the surrounding words of the claim must be considered.

Indeed, Nippon Shinyaku understood how to read these terms in context. As mentioned, they have a product on the market that, just like Sarepta's, is directed to a target region of exon 53 of the human dystrophin pre-mRNA, and has all Ts, or thymines, instead of Us, or uracils.

And what you will see, Your Honor, is that by extracting terming that describe the claimed antisense oligonucleotide from the surrounding claim language, Nippon Shinyaku's constructions either impermissibly broaden the claims, as in the term "a base sequence," or make no sense, as in the context "annealling site." And as the Federal Circuit said, that's why Nippon Shinyaku's approach leads their constructions astray.

Now, Nippon Shinyaku asserts that five separate terms are indefinite. But NS has a high burden; it needs to prove indefiniteness by clear and convincing evidence.

It's also premature to evaluate indefiniteness, Your Honor. As courts in this circuit routinely refrain from reaching indefiniteness at this early stage of the

rendered the term void, meaningless, or superfluous are highly disfavored and should be rejected here.

To the extent that Sarepta has relied in their briefing on sample oligonucleotides, those in table A of the specification and those identified by their experts, as showing that oligonucleotides are commonly referred to as one base sequence, that's unavailing. These are just examples that boast their embodiments, they are not a bases to limit the claims. And the Federal Circuit has long cautioned against that approach.

Here, the claims are much broader than Sarepta's collective construction, and for that reason, NS respectfully requests that this Court reject Sarepta's collective approach.

THE COURT: All right. So Mr. Raich, a few questions on this. How do you respond to NS's position that your -- that Sarepta's proposed collective construction makes the terms comprising -- makes the term comprising, superfluous, and also reads a preferred embodiment into the claims?

MR. RAICH: Yeah, thank you, Your Honor. Can we have slide 11, please, from our presentation.

So comprising the -- in Sarepta's construction allows for other elements. And so, for example, there's a base sequence, so it's comprising a base sequence, but

comprising is an open term. And so, for example, Sarepta's construction allows for the backbone sequence in the oligonucleotide or would allow for what we call a five prime cap at the end of the oligonucleotide.

So Sarepta's construction is not reading the term comprising out of -- at all, it allows for other things. What it requires is that the base sequence be the base sequence of the entire oligonucleotide. And I think we're going to discuss that more in the context of the 1A construction, so I'm going to continue on this theme because I think Your Honor has hit on an important point.

In terms of your question about the reading in embodiments, I mean, it's exactly the opposite. I think that the embodiments in the specification support our construction, support our interpretation. And when all of the examples in, for example, table 1A when there's 211 different nucleotides listed, all with a single base sequence, that is supportive of Sarepta's construction, we're not reading something in.

And, in fact, as I'll discuss momentarily, it's our position that Nippon Shinyaku is actually eliminating the requirement for 100 percent complementarity with their -- with their interpretation of a base sequence being only a portion of the oligonucleotide. And I'd like to go into that in sort of more detail as I walk through the term

"a base sequence," Your Honor.

THE COURT: Let me ask you, before you do that, counsel for Nippon Shinyaku, Ms. Williamson, advised that there are only three terms in this preamble phrase that are in dispute, so why should the Court -- I understand that you're saying it should all be construed in context, but does Sarepta disagree that within that phrase there's really only three terms in dispute?

MR. RAICH: I think that that is a fair statement, that there are three terms that are disputed within this term. And Your Honor is exactly right, it's our position that the terms work together to provide sort of a single concept that a skilled artisan would understand, which is why in our view it makes more sense to construe the term as it stands instead of picking pieces out of it where things can get a little confusing.

THE COURT: Okay.

MR. RAICH: So let's turn to slide 14. And I'm going to tackle now one of the embedded terms, which is the term "a base sequence," and this is sort of a continuation of the discussion that we were just having.

So it is Sarepta's position that this does not need to be construed, it certainly doesn't need to be construed separately. But to the extent Your Honor chooses to construe it, it should be given its plain and ordinary

meaning, which is just a linear sequence of bases.

It's NS's position that the term "a base sequence" means any sequence of bases that is part of the antisense oligonucleotide.

Now, Sarepta's construction requires that the antisense oligonucleotide be 100 percent complementary to its target. NS's construction does not. If there's just a part of the sequence that is complementary, then it would satisfy NS's construction.

Now, first, NS's construction is consistent with the plain claim language. It says, "An antisense oligonucleotide comprising a base sequence that is 100 percent complementary or a linear sequence of bases." So as Dr. Stein explains, in context the base sequence refers to a linear sequence of bases of the claimed antisense oligonucleotide as a whole.

Now, secondly, let's look at what the specification says. Sarepta's construction is consistent with the specification. So the specification includes table 1A, which has a list of 211 oligonucleotides. And it reports the nucleotide sequence or the base sequence of those oligonucleotides. And what's shown is that each oligonucleotide has a single base sequence. And that's shown here on slide 16.

Further, if you look at the specification, the

earlier, if we just look at the claim language, this is technical language so here's maybe an example. If you have something that says, for example, a Christmas tree comprising a trunk that is 100 percent wood, under their construction they would allow that trunk, if something was 50 percent wood and 50 percent plastic, something that was brought in a store, that would be okay, because part of it, 50 percent of it is 100 percent wood. That just doesn't make sense in this context in this art.

The base sequence refers to the base sequence of the oligonucleotide, that's how ever example was shown in the prior art, that's how the examples are in table 1A of the specification. That is consistent with how the term "base sequence" is used in this art.

I also want to talk about the specification and its warning. So as Sarepta's expert explained, under NS's construction, the antisense oligonucleotide could only have those 12 bases that I mentioned, which is -- if you have an oligonucleotide that's 31 nucleotides in length, that's less than 40 percent of the oligonucleotide that is complementary.

But the specification warns against using antisense oligonucleotides with insufficient complementarity to avoid nonspecific binding of antisense compounds to non-target secrets. So the specification guides that there

must be a sufficient degree of complementarity to avoid non-specific binding.

Their construction allows for very low levels of complementarity, but a skilled artisan is deemed to read the claim term not only in the context of the particular claim which the disputed term appears, but in the context of the entire patent, including the specification.

Now, NS suggests that an embodiment called a weasel supports its construction. This does not -- I just used the word "weasel" in the context of the case, this is a totally separate thing, so not to be confusing.

So the weasels are not encompassed by the asserted claims, and that's just fine. Patents are allowed to have alternative embodiments, some of which are encompassed by constructions and some of which are not. And we shouldn't contort the construction to try to reach something that's clearly not intended to be covered by the claims at issue.

So, first of all, the weasel is identified as three separate oligonucleotides, and the specifications says that you can join together multiple oligonucleotides to create a weasel, whereas the claim is drawn to "an antisense oligonucleotide." So that's the difference.

Separately, the weasel in the specification is 75 bases long, whereas the claim is drawn to something

that's 20 to 31 bases long.

The weasel targets intron sequence, whereas the claims are directed to targeting exon 53. So you put all of this together and the disclosure of the weasel is an unclaimed embodiment that is not relevant to the construction of these claims.

NS also looks to the prosecution history, and I want to address this briefly. So this is from the prosecution history of the Wilton patent. And the applicant was describing an oligonucleotide called H53A AON1, which it contended was a 18-mer oligonucleotide having a sequence identical to three nucleotides of SEQ ID NO: 195. That's all it says.

Now, NS contends that this defines the term "base sequence" in the claims, but this is not -- the claim term "base sequence," it just says a sequence. It's not discussing the claim term "base sequence." And it doesn't say that there are more than one base sequences in this 18-mer, it's simply saying that three nucleotides of the 18 are identical to another sequence.

So, further, if you look at the same response, NS ignores that applicant depicted the prior art oligonucleotide as having a single nucleotide sequence, a single base sequence that was 18 bases long. And explained that it had only three bases of SEQ ID NO: 195, not that it

has multiple bases in the same oligonucleotide.

So Sarepta's construction, should the judge choose to construe this term, should be adopted. It is supported by the claim language, including the 100 percent complementarity limitation. It's supported by the specification's embodiments and the expressed guidance, and it follows the common use in the art.

THE COURT: Ms. Williamson, a few questions for you to clarify some things.

So how does NS respond to Sarepta's position that there is always a one-to-one correlation between an antisense oligonucleotide and its base sequence?

MS. WILLIAMSON: So, Your Honor, we -- we just don't believe that is the case. So, first, just to give a little background, I will turn to slide 17 of our presentation, so this is something that counsel made quite a bit of argument about. The antisense oligonucleotide of 20 to 31 bases comprises a base sequence.

So we think that's very important because, first, comprising is open-ended, and second, because -- as Your Honor pointed out, because of the modification of the "a base sequence." It also has additional requirements in the claim, that base sequence comprises at least 12 consecutive bases of SEQ ID 195. We all agree to that.

So the minimum base sequence within the claim is

deprotecting agent. But, again, nothing in the claims or the specifications suggest that such indirect reactions are allowed, either under the plain claim language or the sole embodiment disclosed in the specification.

NS's counsel argue that somehow it is wrong that Sarepta's construction read out this method B. But respectfully, there's nothing that the come -- that NS's claim cannot cover method B under Sarepta's constructions. The claim says what it says, and the claims as written should be construed, as the Federal Circuit explained in the *Chef America*.

And for those reasons, Sarepta's construction should be adopted because it is based on the plain claim language and is also consistent with the intrinsic evidence, including the sole embodiment in the specification, and that's how the skilled artisan would have understood, as explained by Dr. Pentelute.

THE COURT: All right. I understand your argument.

MR. MILLER: Just a few very quick points, Your Honor. First, my opposing counsel mentioned the fact that the claims have lettered steps and numbered compounds, and argued that those letters and numbers imported a -- implied a step order.

Your Honor, respectively, those letters and

numbers are used for organizational purposes, so that in later dependent steps, instead of reciting the entire step, the dependent claim -- I'm sorry, in dependent claims, instead of reciting an entire step from the independent claim, the independent claim can simply identify step E as the one being further modified, or other steps like that.

And the same reason those numbered compounds are provided numbers, so you can use a shorthand instead of repeating the structure of each numbered compound every single time it's used, you can just recite to the earlier numbered structure.

I'd also like to pull up slide 21 from my opposing counsel's presentation. And I think this generally shows the improper way that -- that Sarepta has construed these claims. Sarepta is -- if you look at the claims themselves, they say "reacting said Compound 3. And reacting said Compound 4."

Instead of looking at that claim language, Sarepta is importing the underlined limitations from the specification, from an embodiment in the specification that Compound 3 must be produced in step B or produced in step C into the claims themselves.

And we already know that importing limitations from the specification, from an embodiment in the specification, even if it is the only embodiment in the

specification, that's improper. And for those reasons, NS's proposed construction should be adopted, Your Honor.

THE COURT: All right.

MR. MILLER: Thank you.

THE COURT: Thank you.

All right. The Court wants to thank counsel on both sides for your presentations today. The Court will take these matters under advisement and issue a *Markman* ruling as soon as it can. We've been trying to get them out within 60 days, so we will do our best in keep that up.

So with that, that's all I had on the agenda for the day for these parties, so with that we are adjourned.

(Whereupon, the following proceeding concluded at 1:13 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Michele L. Rolfe, RPR, CRR

U.S. District Court

Exhibit 2 to NS's Response to Sarepta's MIL No. 3

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

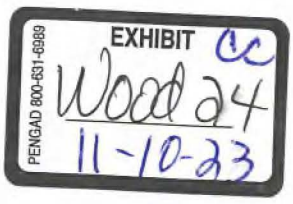
University of Western Australia,
Junior Party
(Patent 8,455,636,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)
v.
Academisch Ziekenhuis Leiden,
Senior Party
(Application 11/233,495,
Inventors: Garrit-Jan Boudewijn van Ommen, Judith Christina Theodora van Deutekom, Johannes Theodorus den Dunnen and Annemieke Aartsma-Rus).

University of Western Australia,
Junior Party
(Patents 7,960,541 and 7,807,816,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)
v.
Academisch Ziekenhuis Leiden,
Senior Party
(Application 13/550,210,
Inventor: Judith Christina Theodora van Deutekom).

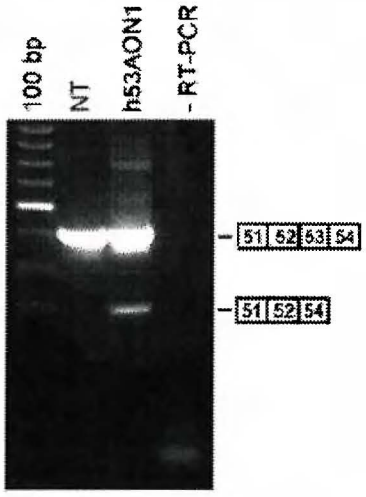
University of Western Australia,
Junior Party
(Patent 8,486,907,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)
v.
Academisch Ziekenhuis Leiden,
Senior Party
(Application 14/198,992,
Inventor: Judith Christina Theodora van Deutekom).

Patent Interference Nos. 106,007, 106,008, 106,113 (RES)
(Technology Center 1600)

DECLARATION OF MATTHEW J. A. WOOD, M.D., D. PHIL.



UWA EXHIBIT 2081
University of Western Australia
v.
Academisch Ziekenhuis Leiden
Interference Nos. 106,007, 106,008 & 106,013



(Adapted from Exh. 2010, Fig. 1(i).) In this example, exon skipping appears relatively inefficient, as the presence of the large upper band reveals that most of the product contains exon 53. Notably, RT-PCR provides no information as to whether or not dystrophin protein is produced. In the case of DMD, it is the protein, not the RNA, that is necessary to restore muscle function.

F. *In Vitro* Exon Skipping Experiments Are Unpredictable

68. Even in these relatively controlled *in vitro* skipping studies, exon skipping is unpredictable.

69. As stated by the AZL group in a 2001 publication, "[t]he efficacy of AONs is largely determined by their binding affinity for the target sequence. Due to base composition and pre-mRNA secondary or tertiary structure, ***it is difficult to predict which AONs are capable of binding the target sequence***." (Exh. 2012 at 1548; emphasis added.)

70. Similarly, in 2002, the AZL group concluded as follows: "We therefore ***have no insight*** into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus ***the effectivity of any designed AON, will therefore still***

have to be tested empirically in the cells, as was done in this study." (Exh. 2010 at S76; emphasis added.)

71. A 2007 paper co-authored by several members of the AZL group states that "several years after the first attempts at dystrophin exon skipping with AOs [antisense oligonucleotides], ***there are still no clear rules to guide investigators in their design***, and in mouse and human muscle cells *in vitro* ***there is great variability for different targets and exons***." (Exh. 2013 at 807; emphasis added.)

72. In 2009, the AZL group wrote that while existing software programs can facilitate exon skipping AON design, "in general ***a trial and error procedure*** is still involved to identify potent AONs." (Exh. 2014 at 548; emphasis added.)

73. There are numerous examples of this *in vitro* unpredictability. For example, the AZL group reported in 2001 that mAON9 induced exon skipping in cultured mouse muscle cells, but mAON8 did not. These AONs were both made with the same 2'-O-Me-PS chemistry and both apparently bound to their target sequences. Moreover, these AONs substantially overlapped, as both contained the nucleobase sequence "UUAGCUGCUGC" as well as additional nucleobases complementary to the mouse dystrophin gene. Yet one induced skipping of exon 46, and the other did not. (Exh. 2012 at 1548.)

74. Another example was published by Wu and coworkers in 2011. These researchers screened a series of AONs covering more than two thirds of human dystrophin exon 50 and two flanking intron sequences. A subset of the tested sequences, all made with 2'-O-Me-PS chemistry, is shown in the Table below:

Name	Target[2]	2'-O-Me-PS AON Sequence	Length	Effect
AO3PS	-19+1	UCUUUAACAGAAAAGCAUAC	20	-
AO4PS	-19+3	CCUCUUUAACAGAAAAGCAUAC	22	4%
AO5PS	-19+8	AACUUCCUCUUUAACAGAAAAGCAUAC	27	21%
AO6PS	-19+13	CUUCUAACUUCCUCUUUAACAGAAAAGCAUAC	32	3%

(Exh. 2015 at 4.) The 20-mer AO3PS induced no detectable exon skipping. The 22-mer AO4PS, differing only in having two additional nucleotides complementary to the *DMD* gene, induced detectable exon skipping in 4% of cells. Adding an additional five nucleotides increased exon skipping to 21%. However, adding five more nucleotides largely abrogated this effect. Consistent with this, the AZL group noted in a 2009 publication that increasing AON length could decrease exon skipping efficiency. (Exh. 2014 at 552.) The observations on AON length versus skipping efficiency reported by Wu *et al.* are consistent with my experience. AONs have an optimal length, which is a result of a number of factors including nucleotide sequence, chemical modifications, and target accessibility, and when that length is either not reached or is exceeded the skipping efficiency drops off. Consequently, I would expect that the great majority of longer AONs, on the order of 50 nucleotides or longer, will not efficiently induce skipping for a number of reasons, if they induce it at all, to be useful as therapeutic agents for treating DMD. Those reasons include access to the complementary sequence in the pre-mRNA, binding affinity of the AON for the complementary sequence, and the ability to transfect longer AONs into cells.

75. Heemskerk and coworkers, another publication from the AZL group, also highlights this unpredictability. (Exh. 2020 at 259-60.) For example, Heemskerk analyzed exon skipping by RT-PCR of mouse exon 23 with a "short" 2'-O-Me-PS AON that was 20 nucleotides

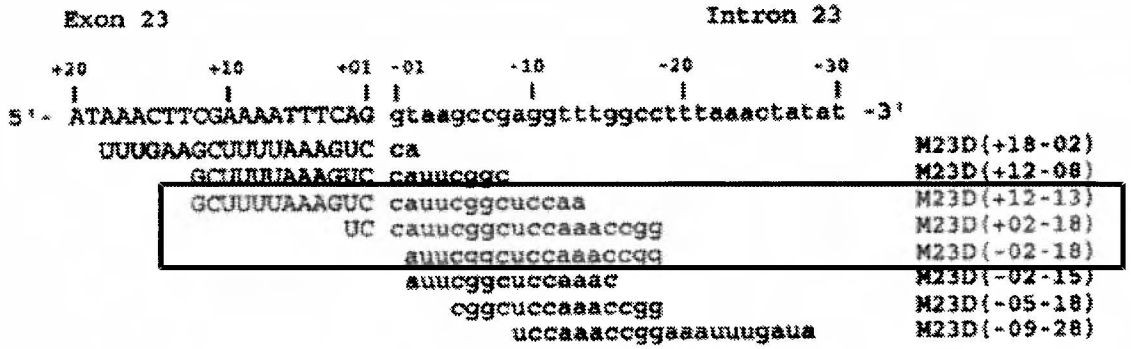
[2] The Target column shows the coordinates of the target site relative to the pre-mRNA sequence. "+" represents an exonic position and "-" represents an intronic position, with the numbers representing the first and last nucleotides AON target sequence. (Exh. 2015 at 4.)

in length, a "long" 2'-O-Me-PS AON that was 25 nucleotides in length, and the "long" AON made as a PMO. The sequences of these AONs are shown below.

Name	AON Sequence (3' to 5')	Length
m23AON5'ss	UCCAUUCGGCUCCAAACCGG	20
m23AON5'sslong	UAAAGUCCAUUCGGCUCCAAACCGG	25
m23PMO5'ss	TAAAGTCCATTCGGCTCCAAACCGG	25

According to the authors, "[t]he PMO induces significantly higher levels of exon skipping than both [2'-O-Me-PS] AONs." (Exh. 2020 at 259.) But "[t]he long [2'-O-Me-PS] is significantly less efficient than the short version." (Exh. 2020 at 259.) This data shows the complex interactions between nucleotide length, nucleotide sequence, internucleotide linkages, and chemical backbone, and reinforces the need for empirically testing each chemically distinct AON.

76. Another study, authored by Dr. Wilton's group at UWA, examined skipping of exon 23 from the mouse DMD gene by RT-PCR following transfection with a series of overlapping 2'-Me-O-PS AONs, as shown in the following figure. Of the AONs tested, only M23D(+12-13), M23D(+02-18), and M23D(-02-18) were effective in inducing detectable exon skipping. (Exh. 2017 at 647.)



(Exh. 2017 at 646.) Notably, the shorter AON M23D(-02-18), which is only 17 nucleotides in

length, was particularly efficient at inducing skipping and was reported to induce exon skipping at concentrations as low as 5 nM. The authors concluded that they could improve "the efficiency of the technique" by "reduc[ing] the size and the effective dose of the AO[N]s" examined. (Exh. 2017 at 644.)

77. Arechavala-Gomeza and colleagues investigated eight specific AON sequences targeting human DMD exon 51 using two different chemical forms (2'-O-Me-PS and morpholino) in human muscle cells, human muscle explants, and human muscle explants from patients with DMD. (Exh. 2013 at 798.) Five AONs targeting the 5' splice site were "surprisingly" determined to be largely ineffective at inducing skipping of exon 51. (Exh. 2013 at 803.) Three other overlapping sequences complementary to potions of exon 51 were each capable of inducing exon 51 skipping in cells from healthy patients, including sequence B30 (targeting +66+95) and A20 (targeting +68+87. (Exh. 2013 at 803.) But B30 induced significantly better exon skipping in cells derived from a DMD patient with a deletion in exons 48 and 50 than A20. (Exh. 2013 at 805 ("the skip achieved with AO A20 was less efficient").) Similarly, B30 induced significantly better skipping in cells derived from a DMD patient with a deletion in exon 50 than A20. (Exh. 2013 at 805 ("the percentage of the skip was 13% for AO[N] A20 and 73% for AO[N] B30.") This shows that both nucleobase sequence and target cell type influence exon skipping.

78. Several factors complicate analysis of these and other studies. First, different AONs show varying effectiveness on different cell types (for example, cells from healthy individuals or DMD patients), as was observed in the Arechavala-Gomeza publication discussed above. Those authors report that "the very nature of this targeted exon skipping approach makes it impossible to test many of the specific sequences to be used in humans in healthy volunteers,

because of the potential for disrupting the intact dystrophin open reading frame, leading to nonfunctional dystrophins." (Exh. 2013 at 808; *see also* Exh. 2018 at 909.) Similarly, an AON that appears to have activity on one type of patient cells, such as skeletal muscle, may not have activity in other types of patient cells, such as cardiac muscle for reasons such as the ability of AONs to penetrate the respective cell types. (Exh. 2005 at 179.)

79. Second, *in vitro* exon skipping studies often use transfection reagents such as PEI that in essence form nanoparticles. It is impossible to know the actual AON dose administered to cells because these particles form suspensions. Complicating matters further, different reagents are used for transfecting cells with AONs having different chemical backbones, undermining "dose" and "efficiency" comparisons across studies. For example, we have recently shown that the *in vivo* activity of anionic AONs is correctly modeled *in vitro* only when using gymnotic delivery, that is, transfection of the AON into cells in the absence of a delivery agent like PEI. (Exh. 2011.)

80. Third, even *in vitro*, it is difficult to extrapolate results from one AON class (for example, a morpholino) to another. Because different AON chemistries influence binding affinity, each type of AON will have different binding characteristics, even with identical nucleobase sequences. This is reflected in the optimal lengths observed for AONs of different types: although there may be exceptions, in my experience, the typical length for an exon skipping 2'-O-Me-PS is 18-20 nucleotides; the typical length for a morpholino is 22-30 nucleotides; the typical length for a PNA is 22-25 nucleotides; and the typical length for an LNA is 13-18 nucleotides. Thus, if one attempted exon skipping with a morpholino AON using a nucleobase sequence that induced *in vitro* skipping when contained in a LNA AON, it would be unlikely to work. Conversely, if one attempted exon skipping with a LNA AON using a

nucleobase sequence that induced *in vitro* skipping with a morpholino AON backbone, it also would be unlikely to work, and moreover would likely bind to other parts of the genome because of the relatively high binding affinity of LNAs.

81. I am not aware of anyone testing any AONs of longer than 40 nucleotides in any exon skipping assay, regardless of AON chemistry.

G. Mismatches Unpredictably Alter Efficacy of AON Exon Skipping Activity

82. A mismatch occurs when there is a discrepancy in the Watson-Crick base pairing of the AON and the target pre-mRNA. Several studies have evaluated the effects of mismatches on exon skipping.

83. One study evaluated AONs designed against exon 19 of the mouse DMD gene in inducing skipping of the human DMD gene. With the exception of one AON containing seven mismatched bases, all mouse-specific AONs induced exon 19 skipping in human cells. However, 20- to 100-fold higher concentrations of mismatched 2'-O-Me-PS AONs were required as compared to perfectly complementary AONs. This was believed to result from the reduced annealing potential caused by the mismatched nucleobases. (Exh. 2004 at 525.)

84. Another study evaluated a panel of AONs designed to skip exon 25 from human dystrophin in normal and dystrophic patient cells. While the investigators expected that a single mismatch mutation would compromise AON binding and efficiency, the mismatched AON actually induced exon skipping *more* efficiently than a perfectly complementary AON (Exh. 2019 at 5.) As stated by the investigators, "most unexpectedly, H25A(+95+119), which annealed across the insertion and was therefore mismatched, induced the most robust exon skipping." (Exh. 2019 at 5.) In some instances, mismatches can therefore increase exon skipping efficiency.

523. I understand that the real parties in interest are Academish Ziekenhuis Leiden and its licensee Prosensa Therapeutics, and the University of Western Australia and its licensee Sarepta Therapeutics. I do not have any financial interest in any of these parties or in the outcome of this proceeding.

524. I believe that I can provide an independent opinion in this matter as an independent expert witness.

XIII. PRIOR EXPERT TESTIMONY

525. I have not provided expert testimony in any proceeding as of the date I signed this declaration.

526. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

527. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I also declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

11/18/2014
Date

Matthew J. A. Wood, M.D., D. Phil.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	)	C.A. No. 21-1015 (JLH)
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	)	

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S REPLY IN SUPPORT OF MOTION *IN LIMINE* NO. 3 TO EXCLUDE CERTAIN EXPERT TESTIMONY OF MICHELLE HASTINGS PH.D.

Dr. Hastings' § 112 Opinions. NS does not dispute that Dr. Hastings ignores the claim term "antisense" in her written description and enablement analyses of the Wilton Patents. NS acknowledged during *Markman* that "base sequence" (the term actually construed) and "antisense" are ***not*** the same thing. Hr'g Tr. (May 3, 2023) at 12:24-13:1. The Court agreed. D.I. 248 at 10-11 ("the patentee chose to recite 'a base sequence' as a separate claim term from 'antisense oligonucleotide,' which suggests that ***the two terms have distinct meanings***."). NS is therefore wrong that Dr. Hastings "directly applied the Court's construction" (Br. 1) because the Court did not suggest the term "antisense oligonucleotide" could be ignored. It is irrelevant that Sarepta understood that NS was planning to argue that the remainder of the claimed "antisense oligonucleotide" could be completely random. This does not absolve NS's expert of an obligation to consider the meaning of the world "antisense." The cases NS cites regarding rearguing unsuccessful claim construction to the jury (Br. at 2) are inapposite because the *Markman* ruling did not address "antisense."

NS's argument that "antisense" can be ignored because it is in the preamble is a red herring. The term "antisense" is repeated multiple times in the ***body*** of each asserted claim, provides antecedent basis and is an essential structural limitation in the body of the claims, and the specification underscores the importance of "antisense." *E.g.*, D.I. 417-1 at 1:40-42. Further, "antisense" is ***only in the body*** (not the preamble) of most asserted claims.

Dr. Hastings' Reliance on Dr. Wood. NS's only argument is that Dr. Hastings should be permitted to rely on Dr. Wood's declaration from a prior interference proceeding because it is public. Even aside from Dr. Wood's sworn statement not to opine on invalidity, it is improper to rely on hearsay statements from a different expert in a different proceeding. *See Merck Eprova AG v. Gnosis S.P.A.*, No. 07 CIV. 5898 RJS, 2011 WL 10818492, at *2 (S.D.N.Y. June 8, 2011).

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April 29, 2024

CERTIFICATE OF SERVICE

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